Remarks

In the previous Office Action of 11/01/2007, the Examiner made a restriction requirement FINAL and examined the elected Group II claims 91-139 that are drawn to oligonucleotides.

The Examiner rejected claims 91-139 under 35 USC 112, 2nd paragraph for indefiniteness, 35 USC 101 for being directed to nonstatutory subject matter and 35 USC 103 for obviousness. Claims 140-166 are also rejected under 35 USC 103 for obviousness.

The following Remarks are directed to each the above points of rejection. The points of rejection will be remarked upon in the order in which they appear in the Office Action on 11/01/2007.

Regarding the indefiniteness rejections of claims 91-139 under 35 USC 112, 2nd paragraph

The applicants respectfully submit that no true case of prima facie indefiniteness has been made with respect to claims 91-139, and respectfully submit that each of claims 91-139 is definite for a person of ordinary skill in the art of linkage studies (and neighboring arts) when read in light of the specification.

Regarding claim 91, the Examiner states *"..it is unclear (a) in what way the method of choosing the markers further limits the claimed composition, and (b) in what way the recited limitations of the CL-F further limit the claimed composition."*

The applicants respectfully take issue with the Examiner's finding of prima facie indefiniteness, and respectfully submit that claim 91 is definite for a person of ordinary skill in the art of linkage studies (and neighboring arts) when read in light of the

specification. Claim 91 recites *"A composition comprising a set of oligonucleotides,... complementary to a group of two or more bi-allelic covering markers."* Since the oligonucleotides are complementary to the covering markers, the covering markers therefore determine the oligonucleotides in a definite way, see [0146]. These complementary oligonucleotides have utility in obtaining genotype data (and sample allele frequency data) at the "two *or more bi-allelic covering markers,"* see paragraphs [0251]-[0253]. Complementary oligonucleotides for use in genotyping (or obtaining sample allele frequency data) are well known in the art, see [0248]-[0250]. The applicants have also amended independent composition claim 91 to specifically recite the phrase *"for use in obtaining genotype data or sample allele frequency data,"* see Remarks below under the 101 rejection. **The chosen group of covering markers thus determines or defines the claimed set of oligonucleotides and composition in a definite way.**

The group of covering markers of the claim is clearly set forth in the application and is definite for a person of ordinary skill in the art of linkage studies when the claim is read in light of the specification. In addition the components of the claim are also clear and definite. The applicants direct the Examiner especially to application paragraphs [0046]-[0052] and [0065]. A CL-F region is defined as a collection of one or more points on a CL-F map [0050], each point in the region is the possible location of a trait-causing polymorphism [0065] (or "gene" [0007]). The CL-F map is like an x-y graph and has axes of chromosomal location and population least common allele frequency [0046].

The *"group of covering markers is chosen so that a CL-F region is systematically covered by the covering markers,"* this means one or more of the markers are *close* (in two-dimensions) to each point in the region, see [0049]-[0052], [0079]. Two-dimensional systematic covering defined by two-dimensional closeness ([0042], [0035]) is **readily understood by a person of ordinary skill,** because it is similar to the older conventional "one-dimensional covering" based on one-dimensional

closeness ([0017] – [0020]). In the older conventional one-dimensional covering, markers are chosen so that one or more markers are close (in one dimension) to each point in a one-dimensional region thought to contain a sought trait-causing polymorphism. **Both the old one-dimensional and the new two-dimensional covering increase the chance (or power) to detect linkage through one-dimensional or two-dimensional "closeness" respectively, see [0019]-[0020], [0035], [0042], [0052], [0079].**

The choice of covering markers that systematically cover a CL-F region increases the power of an association based linkage test to detect linkage between a covering marker and a trait-causing polymorphism (or "gene") located at a point in the CL-F region, see [0052], [0079]. The increased power in systematic covering is based on the mathematical principle the inventor discovered: *"The theory of operation is based on the mathematical observation that the TDT and other association-based tests for linkage are increased in power as the frequencies of the disease-*[or trait] *causing allele of a bi-allelic gene and the positively associated allele of a linked bi-allelic marker become similar in magnitude,"* see [0285]. Extensive calculations and observations of the effect of this principle and allele frequency on the power of association-based linkage tests (such as the TDT and others) are contained in the application, see for example [0029], [0285]-[0300] (and [0325.01]-[0325.14] added to the specification in December 2005 through incorporation by reference). More information on systematic two-dimensional covering is given in [0177]-[0183], including examples of two-dimensional closeness distances (covering distances) to achieve systematic covering are also given (see for example [0180], [0181], [0192], [0223] and [0226]).

Thus the group of covering markers recited in the claim is definite to a person of ordinary skill in the art of linkage studies when read in light of the specification. Because the group of covering markers is definite, the set of complementary oligonucleotides and composition of the claim are also definite. See also MPEP

2173.02 which essentially indicates claim terms are definite when the terms' components are definite, citing Bancorp vs. Hartford that states *"the components of the term have well recognized meanings, which allow the reader to infer the meaning of the entire phrase with reasonable confidence."*

The Examiner uses the phrases *"further limit"* and *"further limits"* in the rejection of claim 91 for indefiniteness. The applicants respectfully caution the Examiner that MPEP 2173.04, Breadth Is Not Indefiniteness, states *"Breadth of a claim is not to be equated with indefiniteness."* The applicants also respectfully point out that there are other limitations in claim 91 not mentioned in the indefiniteness rejection, such as *"thousands of bi-allelic markers"* and *"covering markers with least common allele frequencies less than or equal to 0.3."*

Regarding the indefiniteness rejection of claim 92, the Remarks above under claim 91 are relevant to claim 92 and the Examiner is urged to read those Remarks. Regarding rejection part (a), the limitations of the CL-F region recited in claim 92 are definite. The claim recites *"the CL-F region is for the species of creatures and for a population, wherein the population is a population as in the field of population genetics."* The terms CL-F map and CL-F region are clearly defined in the application, and are definite, see [0046], [0050] and [0064]-[0065], [0075].

Though the terms CL-F map and CL-F region are "new", as MPEP 2173.05(a) II states: *"Courts have recognized that it is not only permissible, but often desirable, to use **new terms** that are frequently more precise in describing and defining the new invention. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Although it is difficult to compare the claimed invention with the prior art when new terms are used that do not appear in the prior art, **this does not make the new terms indefinite**."*

The concepts of a two-dimensional CL-F map and CL-F region are readily understood by, and definite to, a person of ordinary skill in the art of linkage studies. These

concepts are similar to conventional art concepts of a one-dimensional (chromosomal location) map and region, see [0019], [0020] and [0175], [0176]. Indeed information that may be used to construct a CL-F map and CL-F region is available from sources that have conventional one-dimensional (chromosomal location) maps, such as the Whitehead Institute or Marshfield Foundation, see [0175] and [0176].

Regarding rejection part (b), the species and population limitations of the CL-F region recited in claim 92 are definite. The chromosomal locations of polymorphic markers and least common population allele frequencies from sources such as Whitehead or Marshfield (see [0175] & [0176]) are generally **for particular populations of a particular species, wherein the populations are populations as in the field of population genetics**. The "F axis" in "CL-F" stands for "Frequency" and is short for "least common allele frequency" or "least common **population allele frequency**." The term population is also described and defined in the last sentence of [0135].

The present patent application is entitled Two-Dimensional Linkage Study Techniques and is directed to linkage study techniques. A person of ordinary skill simply knows that linkage studies are, or almost always (or generally), done for particular species and populations, wherein the populations are populations as in the field of population genetics. The concepts of CL-F map and CL-F region are for use in such linkage studies. Therefore the phrase *"the CL-F region is for the species of creatures and for a population, wherein the population is a population as in the field of population genetics"* is clearly definite to a person of ordinary skill in the art.

Regarding part (c) of the rejection, the applicants respectfully submit that the limitation in question (*"the largest chromosomal length, computed by any method, for which linkage disequilibrium has been observed between any polymorphisms in any population of the species"*) is a definite number.

Regarding the indefiniteness rejection of claim 94, see Remarks above under claims 91 and 92.

Regarding the indefiniteness rejection of claims 104, 108 and 110, see Remarks above under claims 91 and 92. For the term "segment-subrange" in claims 104 and 108, see also [0090] and [0185]. A segment-subrange is simply a rectangular region on a two-dimensional CL-F map and is definite to a person of ordinary skill.

For other limitations in claim 110 regarding sets and subsets of markers, see [0301] and [0306]. The choice of covering markers in [0306] uses concepts that are familiar and definite to a person of ordinary skill in the art of linkage studies and the method of choosing markers is therefore definite. The Examiner is also directed to the Figure (Illustration of an Example Set/Subset N-covering using a CL-F map) with Explanation on page 14 of Miscellaneous Incoming Letter of November, 21, 2005 in the Image File Wrapper for the application.

Regarding the indefiniteness rejection of claims 91-94, 104, 108 and 110, the Examiner states: *"it is unclear as to the metes and bounds of 'CL-F region' and a 'CL-F map'."* The Examiner is directed to Remarks above under claims 91 and 92; some of these Remarks are now reproduced again below.

The terms CL-F map and CL-F region are clearly defined in the application, and are definite, see [0046], [0050] and [0064]-[0065], [0075].

Though the terms CL-F map and CL-F region are "new", as MPEP 2173.05(a) II states: *"Courts have recognized that it is not only permissible, but often desirable, to use **new terms** that are frequently more precise in describing and defining the new invention. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Although it is*

difficult to compare the claimed invention with the prior art when new terms are used that do not appear in the prior art, ***this does not make the new terms indefinite****."*

The concepts of a two-dimensional CL-F map and CL-F region are readily understood by, and definite to, a person of ordinary skill in the art of linkage studies. These concepts are similar to conventional art concepts of a one-dimensional (chromosomal location) map and region, see [0019], [0020] and [0175], [0176]. Indeed information that may be used to construct a CL-F map and CL-F region is available from sources that have conventional one-dimensional (chromosomal location) maps, such as the Whitehead Institute or Marshfield Foundation, see [0175] and [0176].

Regarding the indefiniteness rejection of claims 111-123, and 133-139, in response to this rejection the applicants have amended claims 111-123.

The Examiner cites MPEP 2173.05 in this rejection and states: *"It is noted that a single claim that recites both a product and apparatus (i.e. for producing the product) in the same claim are considered indefinite [MPEP 2173.05]."* It is unclear, however, to which subsection of MPEP 2173.05 the Examiner refers. The word "apparatus" appears only in MPEP 2173.05 subsections (b), (p) and (v). None of these subsections refer to a single claim reciting both a product and an apparatus for producing the product. The closest passage appears to be MPEP 2173.05 (p) II PRODUCT AND PROCESS IN THE SAME CLAIM. **The applicants respectfully request that the Examiner further clarify the rejection because of the apparent discrepancy cited above.**

Regarding the rejection of claims 91-139 under 35 USC 101

The Examiner has rejected these claims for "reading on" nonstatutory subject matter, specifically *"the naturally occurring genome of 'any creature'"* and *"a human being."*

The applicants do not regard their invention as *"the naturally occurring genome of 'any creature'"* or *"a human being."* The Examiner is directed to parts of the application that

are generally relevant to the claimed invention, specifically paragraphs [0264]-[0267], and supporting parts [0258]-[0262], [0244]- [0257] (Oligonucleotide Technology) and [0140]-[0146]. There are, for example, no examples of *"the naturally occurring genome of 'any creature'"* or *"a human being"* cited under Oligonucleotide Technology, paragraphs [0244]- [0257]. None of the example technologies cited under Oligonucleotide Technology, paragraphs [0244]- [0257], is "naturally occurring."

In addition, the application describes the *utility* of the described complementary oligonucleotides (and compositions comprising the oligonucleotides) for obtaining genotype data and sample allele frequency data for use in linkage studies; see [0266] and also for example [0255], [0259], [0260], and Oligonucleotide Technology ([0244]-[0250]). ***In its natural state***, a *"naturally occurring genome of any 'creature'"* does not have utility for obtaining genotype data or sample allele frequency data. In addition, the applicants have amended independent composition claim 91 to specifically recite the phrase *"for use in obtaining genotype data or sample allele frequency data."*

Claim rejections under 35 USC 103

Claims 91-166 are rejected under 35 USC 103(a) as being unpatentable over Cohen (US Patent 5945522), in view of Kruglyak (Am. J. Hum. Genet., 1995, vol. 57, pp. 439-454) .

The applicants respectfully disagree that the cited references render the claimed inventions prima facie obvious. The following are some of the reasons a person of ordinary skill in the art of linkage studies would recognize that the cited references do not render the claimed inventions prima facie obvious. The (or a) very important reason is given first.

Firstly, the Examiner correctly notes (page 7 of the Office Action) that the method of choosing markers in Cohen chooses "informative markers." Specifically the Examiner correctly states: *"Thus, the bi-allelic markers selected by this method will be*

'informative markers' since they have a frequency of 0.3 to 0.5 for the minor allele and 0.5 to 0.7 for the major allele." The Background of the present application refers (e.g., paragraph [0026]) to such conventional methods of choosing such "informative" bi-allelic markers (with minor allele frequencies ≥ 0.3) for linkage studies. Paragraph [0026] states: *"The greatest information content is given by bi-allelic markers with allele frequencies close to the optimum of 0.5/0.5. ... Secondly, bi-allelic markers with lower least common allele frequencies, less than 0.3(0.7/0.3) or 0.2(0.8/0.2), are viewed unfavorably for linkage studies in this* [conventional Kruglyak] *reference."* (For the Examiner's benefit, it should be noted that the terms "least common allele" and "minor allele" of a bi-allelic marker or bi-allelic polymorphism mean the same thing.)

By contrast, the inventor discovered that use of bi-allelic markers with lower least common (or minor) allele frequencies in association based linkage studies, has an important, major unexpected result. Specifically, for example, paragraph [0035] right column states, *"In addition, the inventor's calculations and observations indicate that bi-allelic markers having least common allele frequencies less than 0.3, 0.2 or even less than 0.1 have an important place in linkage studies using association based linkage tests. This is markedly different than Kruglyak's information content evaluation of bi-allelic markers for use in linkage studies, in which bi-allelic markers with least common allele frequencies less than 0.3 or 0.2 are viewed unfavorably."* **The Examiner is directed to the claim limitation, *"wherein there are covering markers with least common allele frequencies less than or equal to 0.3",* in independent composition claim 91.**

The major unexpected result is an increase in the power of an association-based linkage test to detect linkage between covering markers with low least common (or minor) allele frequencies and a trait causing polymorphism with a least common (or minor) allele frequency of similar (e.g., low) magnitude. Details of this unexpected power result are contained in the application. Some examples of these details are described and explained on page 21 in paragraphs [0285]-[0289] and

Table 2. In Table 2 the least common (or minor) disease-causing (trait-causing) allele has a low frequency of p = 0.1; and the least common (or minor) allele frequency, m, of an associated marker allele *varies* between 0.5 and 0.05. The table shows that (for each value of penetrance ratio (r) and disequilibrium (δ)) the "signal strength," P_t, increases substantially and is highest for values of m close to 0.1. The highest value of P_t occurs when m=p=0.1. **Note that high values of P_t (and power) occur for markers with minor allele frequencies, m, less than or equal to 0.3.** Paragraph [0289] states: *"This sort of substantial increase in power is also true of other association-based linkage tests as the frequencies of the disease-causing allele and associated marker allele become more similar in magnitude."*

And earlier paragraph [0286] explains, *"P_t may be regarded as the size of the 'signal' which is given by the TDT to indicate that a tested marker is linked to a disease-causing gene. The more P_t is elevated above 0.5 (baseline), the greater is the evidence for linkage or 'power' provided by the association-based linkage test known as the TDT."*

And an even earlier paragraph [0285] gives the general principle: *"The theory of operation is based on the mathematical observation that the TDT and other association-based tests for linkage are increased in power as the frequencies of the disease-causing allele of a bi-allelic gene and the positively associated allele of a linked bi-allelic marker become similar in magnitude."* This general principle applies, of course, to any trait-causing polymorphism (or "gene"), see for example paragraph [0052]. Paragraph [0052] states: *"The inventor discovered that the power of association based linkage tests to detect linkage disequilibrium between a marker and a trait-causing gene (when present) increases greatly when the bi-allelic marker and the bi-allelic gene are located close together on a CL-F map."* A bi-allelic trait-causing gene and marker have similar allele frequencies when they are located close together on a CL-F map. (In the present application the terms "gene" and "trait-causing polymorphism" mean the same thing, see middle [0007].)

The applicants respectfully submit that the above Remarks are a complete response to the Examiner's finding of prima facie obviousness for claims 91-139. (As the Examiner has stated at the bottom of page 2 of the Office Action, claims 140-166 are withdrawn from further consideration.) The applicants will now also respectfully give further considerations or reasons that the finding of prima facie obviousness for claims 91-139 is incorrect.

It should be noted that the second unobviousness reference cited by the Examiner (Kruglyak, Am. J. Hum. Genet., 1995, vol. 57, pp. 439-454), uses an **Information-Content Mapping** approach for marker selection (see Abstract p. 441 and right column p. 443 to p. 447). This **"Information-Content"** approach is essentially the same as (or very similar to) the "Information-Content" approach used in a later published reference by the same author (Kruglyak) cited in the Background of the present patent application. That Information Content approach leads to bi-allelic markers with lower least common allele frequencies (e.g., less than 0.3) being viewed unfavorably. Specifically, to repeat what was stated above (with emphasis added), the paragraph [0035] right column states, *"In addition, the inventor's calculations and observations indicate that bi-allelic markers having least common allele frequencies less than 0.3, 0.2 or even less than 0.1 have an important place in linkage studies using association based linkage tests.* ***This is markedly different than Kruglyak's information content evaluation of bi-allelic markers for use in linkage studies, in which bi-allelic markers with least common allele frequencies less than 0.3 or 0.2 are viewed unfavorably****."*

The Kruglyak reference in the quote from the present patent application above is Kruglyak: The use of a genetic map of bi-allelic markers in linkage studies. Nature Genetics, September 1997, vol.17, pp. 21-24. This reference is cited in the application at the top of paragraph [0026] and in footnote 4. The Kruglyak reference cited by the Examiner in the Office Action (Kruglyak, Am. J. Hum. Genet., 1995, vol. 57, pp. 439-

454) is cited in footnote 5 of paragraph [0026]. Both of these Kruglyak references and the Information Content approach is discussed in [0026] and the applicants respectfully direct the Examiner to [0026] and also again [0035]. These references include the same author, Kruglyak; and the concepts in the references for the art of linkage studies appear to be cumulative. As explained in [0026], these references lead to bi-allelic markers for use in linkage studies with lower minor allele frequencies (e.g., less than 0.3) being viewed unfavorably. Given such a "teaching away" from markers with lower minor allele frequencies, the applicants respectfully submit that the Kruglyak reference cited by the Examiner in the Office Action, either alone or in combination with the Cohen patent, does not render the claimed invention(s) of claims 91-139 obvious.

The applicants also direct the Examiner to the limitation *"wherein the group of covering markers comprises thousands of bi-allelic markers"* in independent claim 91. Such large numbers of bi-allelic markers (thousands) were *theorized* to exist at the time of filing of the application or provisional priority applications. But the applicants believe that (at least in general) thousands of bi-allelic markers were not actually identified and available for use, or used, in linkage studies at the time of filing of the application or provisional priority applications.

The applicants believe the following remarks are germane to the 103 rejection. The Examiner states (bottom p. 7): *"Cohen does not specifically teach limitations directed to the CL-F map or CL-F region (broadly interpreted as a chromosomal genetic map)."* The terms CL-F map and CL-F region are quite different than a "chromosomal genetic map" and are defined in the application, see [[0064]-[0066] and [0075]. The term "genetic map" is currently defined (by the "Talking Glossary of Genetic Terms" of the National Human Genome Research Institute of the National Institutes of Health (NIH) at http://www.genome.gov/glossary.cfm) as follows. *"**Genetic map:** (Also known as a linkage map) a chromosome map of a species that shows the position of its known genes and/or markers relative to each other, rather than as specific physical points on*

each chromosome." This definition of "genetic map" makes no reference to (population) allele frequency, an important part of the concepts of "CL-F map" and "CL-F region." A "CL-F map" and "CL-F region" are essentially "two-dimensional." Population allele frequency effectively amounts to the "second dimension" of a "CL-F map" (and effectively for a "CL-F region"). A "chromosomal genetic map" is essentially a one-dimensional map and is different than a CL-F map.

The Examiner also states (bottom page 7 and top page 8 of the Office Action): *"Kruglyak teaches the use of a chromosomal genetic map of biallelic markers in linkage studies and provides an computer package (MAPMAKER) for multipoint analysis using dozens of markers [See: Abstract, p.441] wherein the map is a two-dimensional map [Fig. 1] and wherein the markers cover various chromosomal positions [Fig. 2]."*

The applicants respectfully submit that the Examiner has misinterpreted this Kruglyak reference for the following reasons. The Figure 1 (p. 441), to which the Examiner refers, is not a two-dimensional map like a CL-F map. Figure 1 is a two-dimensional plot and the vertical (y-axis) is "IBD probabilities." IBD (identical by descent) is discussed at the top right column on page 439 of the reference. Figure 1 is not a two-dimensional map for bi-allelic markers; and IBD probability is far different than allele frequency, the vertical y-axis on a CL-F map. In addition the markers used for Figure 1 are **not bi-allelic markers**. The markers used for Figure 1 *"have five equally frequent alleles,"* see caption Figure 1 on p. 441. **As is well known in genetics and the art of linkage studies, bi-allelic markers have only two alleles,** see for example the last two sentences of paragraph [0007] of the present patent application.
The Examiner also refers to Figure 2 in the quote above in the Office Action. Similarly the markers used for Figure 2 *"each with five equally frequent alleles,"* **are not bi-allelic markers**; see caption of Figure 2 on p. 443.

Conclusion

Claims 1-90 were previously canceled. Claims 91-139 are drawn to the elected invention. The Examiner has withdrawn from consideration claims 140-166. Of the current pending claims, claims 91, 111-123 are currently amended to address the Examiner's points of rejection in the Office Action of November 1, 2007. Remarks that address the Examiner's Office Action of November 1, 2007 have been respectfully submitted. A small entity fee for third month extension under 37 CFR 1.136 (a) is enclosed.

For the reasons advanced above, applicants respectfully submit that the claims are now in condition for allowance and that action is earnestly solicited.

Respectfully submitted,

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